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EXAMINER	
JOIKE, MICHELE K	

ART UNIT	PAPER NUMBER
1636	

NOTIFICATION DATE	DELIVERY MODE
12/01/2008	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/564,512	DI RAGO ET AL.	
	Examiner	Art Unit	
	MICHELE K. JOIKE	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02 September 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-18 and 20* is/are pending in the application.

4a) Of the above claim(s) *15-18 and 20* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-14* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *13 January 2006* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *1/13/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

Applicant's election with traverse of Group I in the reply filed on September 2, 2008 is acknowledged. The traversal is on the ground(s) that no adequate reasons and/or examples have been provided to support a conclusion of patentable distinctiveness between the identified groups. Also, there has not been shown a search burden. The special technical feature common to the claimed inventions classified into Groups I to III is the use of synthetic *rho*- strains of yeast for producing a heterologous RNA of interest (RNA non coded by the yeast mitochondrial genome as defined at page 5, lines 28- 30 of the specification). This special technical feature is novel and not obvious in view of Fox et al., PNAS, 1988, 85, 7288-7292 which discloses a different use of a different synthetic *rho*- strain. Furthermore, the synthetic *rho*- strain disclosed by Fox et al., is used to manipulate the yeast mitochondrial genome of *rho*- strain (introduction of a mutation by recombination) or to complement a mutation in the mitochondrial genome of a *rho*- strain (see the end of the abstract of Fox et al.).

This is not found persuasive because the Examiner disagrees that the special technical feature is a synthetic *rho*- strain, as this is not claimed. The special technical feature is a transformed yeast cell lacking mitochondrial DNA. Fox et al teach a transformed yeast cell lacking mitochondrial DNA. Also, the intended use of the strain is not relevant as Fox et al teach a product. A search burden has not been shown, as it is not required for lack of unity of invention.

The requirement is still deemed proper and is therefore made FINAL.

Claims 15-18 and 20 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on September 2, 2008.

Specification

The disclosure is objected to because of the following informalities:

The specification is objected to as failing to provide proper antecedent basis for the claimed subject matter. See 37 CFR 1.75(d)(1) and MPEP § 608.01(o). Correction of the following is required: claim 4 claims "mitochondrial targeting signal" which is a limitation not found in the specification.

Claim Objections

Claim 4 is objected to because of the following informalities: Lines 3 and 4 have the language "including includes". This is redundant. Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 14 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The term "advantageously" in claim 14 is a relative term which renders the claim indefinite. The term "advantageously" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. There is no explanation in the specification as to why the three steps in claim 14 are advantageous.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1, 2, 5, 7, 8, 11 and 12 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bonnefoy et al in view of Lisowsky et al.

Bonnefoy et al (IDS reference AX, especially pp. 98-101, 104-105 and 109) teach transformation of S. cerevisiae mitochondria. The mitochondria are transformed with a vector carrying an ARG8 reporter gene. Since the vector is transformed and expressed in mitochondria, it is a mitochondrial transcription vector. ARG8 is an auxotrophic mutant that can be expressed in mitochondria. The mitochondria are transformed by microprojectile bombardment. Cells that survive are selected for. Strains that can be used in the transformation are rho- (large deletions of mtDNA) or rho°(lacking mtDNA). A tester strain can also be used, rho+, mit-. The rho+ tester strain can be mated to a rho- strain. After mating, diploids will be produced when grown on a non-fermentable medium, and they teach that the cells can be mated twice. Also, step c_o implies that the crossing does not have to be repeated if the colonies are identified as being mitochondrial transformants. Bonnefoy et al teach using an auxotrophic or drug resistance marker, or a deletion in a region of interest that will allow respiring recombinants to grow, to confirm transformation. They also teach transforming rho° strains with a plasmid containing an origin of replication that allows the plasmid to replicate. However, they do not teach producing a heterologous RNA.

Lisowsky et al (Eur. J. Biochem. 164: 559- 563, 1987, especially p. 559) teach transforming yeast mitochondria with a plasmid comprising a gene which is expressed to produce RNA. The mitochondria were isolated, and then the RNA was isolated from the mitochondria. Absent evidence to the contrary, the DNA encoding the RNA was

under control of a promoter and terminator that are functional in yeast mitochondria, since the RNA was successfully produced in yeast mitochondria.

The ordinary skilled artisan, desiring to produce RNA in yeast mitochondria, would have been motivated to combine the teachings of Bonnefoy et al teaching transformation of S. cerevisiae mitochondria with the teachings of Lisowsky et al teaching transforming yeast mitochondria with a plasmid comprising a gene which is expressed to produce RNA because Bonnefoy et al state that genetic manipulation of S. cerevisiae mitochondria are amenable to in vivo experimental analysis and should provide a useful model for other systems. It would have been obvious to one of ordinary skill in the art to use mitochondria to produce RNA because studying RNA production will allow for a better understanding of how mitochondrial transcription works, and Lisowsky et al teach that the transcription machinery has been difficult to characterize. Given the teachings of the prior art and the level of the ordinary skilled artisan at the time of the applicant's invention, it must be considered, absent evidence to the contrary, that said skilled artisan would have had a reasonable expectation of success in practicing the claimed invention.

Claim 3 is rejected under 35 U.S.C. 103(a) as being unpatentable over Bonnefoy et al and Lisowsky et al as applied to claims 1, 2, 5, 7, 8, 11 and 12 above, and further in view of Dziembowski et al.

Bonnefoy et al and Lisowsky et al teach all of the limitations as described above. However, they do not teach using ΔSUV3 or ΔDSS1 strains.

Dziembowski et al (J. Biol. Chem. 278(3): 1603-1611, 2003, especially p. 1603) teach using ΔSUV3 or ΔDSS1 strains.

The ordinary skilled artisan, desiring to use ΔSUV3 or ΔDSS1 strains in RNA production in yeast mitochondria, would have been motivated to combine the teachings of Bonnefoy et al teaching transformation of S. cerevisiae mitochondria with the teachings of Lisowsky et al teaching transforming yeast mitochondria with a plasmid comprising a gene which is expressed to produce RNA, with Dziembowski et al teaching using ΔSUV3 or ΔDSS1 strains because Dziembowski et al state that inactivation of SUV3 or DSS1 results in respiratory incompetence and eventual loss of the mitochondrial genome. It would have been obvious to one of ordinary skill in the art to use ΔSUV3 or ΔDSS1 strains because Dziembowski et al teach that inactivation of SUV3 or DSS1 leads to strong inhibition of mitochondrial translation. Given the teachings of the prior art and the level of the ordinary skilled artisan at the time of the applicant's invention, it must be considered, absent evidence to the contrary, that said skilled artisan would have had a reasonable expectation of success in practicing the claimed invention.

Claim 4 is rejected under 35 U.S.C. 103(a) as being unpatentable over Bonnefoy et al and Lisowsky et al as applied to claims 1, 2, 5, 7, 8, 11 and 12 above, and further in view of Komiya et al and Hwang et al.

Bonnefoy et al and Lisowsky et al teach all of the limitations as described above. However, they do not teach cells having a chromosomal copy of a gene encoding an RNAP, or a mitochondrial targeting signal.

Hwang et al (J. of Virology 74(9): 4074-4084, 2000, especially p. 4075) teach a viral RNAP integrated into the genome of Pichia. However, they do not teach cells having a mitochondrial targeting signal.

Komiya et al (J. Biol. Chem. 269(49): 30893-30897, 1994, especially 30896) teach using a mitochondrial targeting signal for cytosolic import.

The ordinary skilled artisan, desiring to use a cell having a chromosomal copy of a gene encoding an RNAP and a mitochondrial targeting signal, would have been motivated to combine the teachings of Bonnefoy et al teaching transformation of S. cerevisiae mitochondria with the teachings of Lisowsky et al teaching transforming yeast mitochondria with a plasmid comprising a gene which is expressed to produce RNA, with the teachings of Hwang et al and Komiya et al because Hwang et al state that using this expression system allowed for sufficient amounts of the polymerase, and was easily expressed, at a low cost. It would have been obvious to one of ordinary skill in the art to use a mitochondrial targeting signal because Komiya et al teach that mitochondrial targeting signals are important for the importation of proteins into the mitochondria. Given the teachings of the prior art and the level of the ordinary skilled artisan at the time of the applicant's invention, it must be considered, absent evidence to the contrary, that said skilled artisan would have had a reasonable expectation of success in practicing the claimed invention.

Claim 6 is rejected under 35 U.S.C. 103(a) as being unpatentable over Bonnefoy et al and Lisowsky et al as applied to claims 1, 2, 5, 7, 8, 11 and 12 above, and further in view of Anziano et al.

Bonnefoy et al and Lisowsky et al teach all of the limitations as described above. However, they do not teach that the reporter gene is gene encoding a protein from the yeast respiratory chain.

Anziano et al (IDS ref. AW, especially p. 5396) teach use of the COXII gene as a reporter.

The ordinary skilled artisan, desiring to use a reporter gene that is a gene encoding a protein from the yeast respiratory chain, would have been motivated to combine the teachings of Bonnefoy et al teaching transformation of S. cerevisiae mitochondria with the teachings of Lisowsky et al teaching transforming yeast mitochondria with a plasmid comprising a gene which is expressed to produce RNA, with Anziano al teaching transformation of the COXII gene into yeast, because Anziano et al state that the COXII gene is a convenient selectable marker for primary mitochondrial transformants. It would have been obvious to one of ordinary skill in the art to use the COXII gene as a reporter because Anziano et al teach that now make it possible, to express proteins in mitochondria without having to select directly for them, or to resort to engineering their expression and subsequent import into mitochondria in the nucleus-cytoplasm. Given the teachings of the prior art and the level of the ordinary skilled artisan at the time of the applicant's invention, it must be considered, absent

evidence to the contrary, that said skilled artisan would have had a reasonable expectation of success in practicing the claimed invention.

Claims 9 and 10 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bonnefoy et al and Lisowsky et al as applied to claims 1, 2, 5, 7, 8, 11 and 12 above, and further in view of Fincham.

Bonnefoy et al and Lisowsky et al teach all of the limitations as described above. However, they do not teach co-transformation.

Finch (Micro. Rev. 53(1): 148-170, 1989, especially p. 151) teaches co-transformation in yeast.

The ordinary skilled artisan, desiring to co-transform plasmids, would have been motivated to combine the teachings of Bonnefoy et al teaching transformation of S. cerevisiae mitochondria with the teachings of Lisowsky et al teaching transforming yeast mitochondria with a plasmid comprising a gene which is expressed to produce RNA, with Fincham teaching co-transformation in yeast, because Fincham states that co-transformation is useful for when a gene cannot easily be directly selected. It would have been obvious to one of ordinary skill in the art to use co-transformation because there is a high probability that if the cell will take upon plasmid, it will also take up the second plasmid. Given the teachings of the prior art and the level of the ordinary skilled artisan at the time of the applicant's invention, it must be considered, absent evidence to the contrary, that said skilled artisan would have had a reasonable expectation of success in practicing the claimed invention.

Claim 13 is rejected under 35 U.S.C. 103(a) as being unpatentable over Bonnefoy et al and Lisowsky et al as applied to claims 1, 2, 5, 7, 8, 11 and 12 above, and further in view of Kim et al.

Bonnefoy et al and Lisowsky et al teach all of the limitations as described above. Lisowsky et al teach lysing the cells and centrifuging, but not centrifuging twice.

Kim et al (Cancer Res. 57: 3115-3120, 1997, especially p. 3116) teach lysing cells and centrifuging twice at 750 x g to isolate mitochondria.

The claim would have been obvious because centrifuging twice instead of once is a simple adjustment that was known in the art and would have yielded predictable results to one of skill in the art at the time of the invention.

Claim 14 is rejected under 35 U.S.C. 103(a) as being unpatentable over Bonnefoy et al and Lisowsky et al as applied to claims 1, 2, 5, 7, 8, 11 and 12 above, and further in view of Dziembowski et al and di Rago et al.

Bonnefoy et al and Lisowsky et al teach all of the limitations as described above. However, they do not teach eliminating the contaminating nucleic acids in the presence of a divalent ion-chelating agent and a second buffer comprising RNase. Lisowsky et al do teach lysing the mitochondria in the presence of EDTA, pH 7.6, but not in the presence of a detergent.

Dziembowski et al teach all of the limitations as described above. They also teach lysing mitochondria with a detergent, Triton X-100 and EDTA.

Di Rago et al (J. Biol. Chem. 263(25): 12564-12570, 1988, especially p. 12565) teach isolating mitochondrial RNA using buffers containing EDTA pH 7.4, and DNase. They teach using DNase, but not RNase.

The claim would have been obvious because the buffers used in the references above were well known in the art for lysing of cells and organelles, and isolating RNA. The claim would have been obvious because the substitution of one known element (RNase) for another (DNase) would have yielded predictable results to one of skill in the art at the time of the invention. RNase is well known to degrade RNA.

Allowable Subject Matter

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MICHELE K. JOIKE whose telephone number is (571)272-5915. The examiner can normally be reached on M-F, 9:00-5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christopher Low can be reached on (571)272-0951. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Michele K Joike/
Examiner, Art Unit 1636

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